Remarks

Claims 18 and 25-26 are pending. Support for the amendment to claim 18 can be found on page 4, lines 24-25 of the specification as filed, which recites that "Other mammals such as sheep and rats are contemplated." Support for new claim 26 can be found in the specification on page 1, line 12, and on page 4, line 20. Both recitations disclose that galanin can be human galanin. Furthermore, there is mention throughout the specification of several conditions, such as diabetes mellitus (page 2), Alzheimer's Disease (page 2) and idiopathic small stature and anorexia (both on page 13 of the specification as filed) which would have only been treated in human subjects. On pages 2 and 3 of the specification, there is mention of various methods involving the administration of galanin agonist to "a subject." One of ordinary skill in the art would have considered this term to refer to human individuals.

In the Office Action dated January 28, 2004, the Examiner states that claims 18 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Luo et. al. ("Luo"). The Examiner states that both the instant methods and the prior art methods inherently include the mechanism of nerve regeneration because the galanin used in both methods is the same identical substance and if galanin's inherent properties include stimulating nerve regeneration when applied to damaged peripheral nerves, the prior art anticipates the instant invention.

Applicants respectfully traverse. There is no teaching or suggestion in Luo that a galanin agonist would have been effective in the treatment of peripheral nerve damage in a subject. Luo demonstrates that galanin inhibits spinal cord electrical hyper-excitability in the rat, following nerve section, when administered directly into the space surrounding the bottom part of the

spinal cord. Such spinal cord hyper-excitability is related to the development of chronic pain states, and, as stated by the authors on page 164 of the document, "The block of spinal sensitization following sciatic nerve section confirms galanin's antinociceptive function." The discussion in Luo is limited to pain states and there is no discussion of peripheral nerve damage or of any possible efficacy of galanin in the treatment of such nerve damage. Peripheral nerve damage is in no way synonymous with chronic neuropathic pain. The actions of galanin in inhibiting chronic pain behavior when administered directly to the spinal cord (part of the central nervous system) in no way implies or predicts regeneration of the sciatic nerve (part of the peripheral nervous system).

The current application provides evidence that galanin has the ability to promote functional nerve regeneration. However, it is highly unlikely that such regeneration would have occurred in the animals used by Luo *et al*, since galanin was administered directly onto the spinal cord. It is very unlikely that the galanin peptide would reach the damaged end of the sciatic nerve (which is the furthest component of the peripheral nerve system from the spinal cord). Even if it did reach the damaged end of the sciatic nerve then it would be so diluted that it would be most unlikely to have had a functional effect on nerve regeneration. . Further, the experiment of Luo *et al* was begun one hour after spinal transection, and, as shown in Figure 3 of Luo *et al*, the response was measured over 150 minutes from the start of the experiment. Therefore, the rats were utilized in the experiment for a maximum of 3.5 hours after decerebration and spinal cord section. This short time period would not have been sufficient for functional nerve regeneration to occur in response to the presence of galanin.

In contrast, the present application clearly indicates that, in wild type mice, nerve regeneration does not reach significant levels until at least several days after nerve injury (page 8, lines 10-11of the specification and Figure 5). In addition, functional recovery in wild type mice is not complete until approximately three weeks after nerve injury (Figure 6), indicating that nerve regeneration is a prolonged process. In support of this argument, applicants have included a Declaration providing scientific evidence that no peripheral nerve regeneration took place during the experiment conducted by Luo et al.

As noted in the application, a statistically significant reduction in nerve regeneration was seen after two, four, and six days in galanin receptor knockout mice compared to wild type mice. Therefore, one of ordinary skill in the art would have understood that the method according to the invention would have been carried out over several days, since the loss of bioavailability of galanin in the nerve cells (as the result of the absence of the receptor in the knockout animals) only reduces the possible level of nerve regeneration after several days.

However, in an effort to expedite prosecution, applicants have amended claim 18 to exclude a subject which is a rat. Luo recite data only related to the rat, and therefore, this limitation is sufficient to overcome the 102(b) rejection.

Regarding the insertion of a negative limitation, the MPEP section 2173.05(i) states that:

> The current view of the courts is that there is nothing inherently ambiguous or uncertain about a negative limitation. So long as the boundaries of the patent protection sought are set forth definitely, albeit negatively, the claim complies with the requirements of 35 U.S.C. 112, second paragraph. Some older cases were critical of negative limitations because they tended to define the invention in terms of what it was not, rather than

> pointing out the invention...Any negative limitation or exclusionary proviso must have basis in the original disclosure. *If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims.* (Emphasis added).

Moreover, in *In re Johnson*, 558 F.2d 1008, 194 USPQ 187 (CCPA 1977), the CCPA held that a claim to a genus with the limitation of a negative proviso that did not appear in the original specification complied with the written description requirement (for the purpose of establishing benefit of an earlier filing date to overcome a prior art rejection based on applicants' earlier foreign-filed patent). The negative proviso, which was inserted to avoid having the claim read on a lost interference count, literally excluded more than the two species disclosed in the application (and the full scope of the negative proviso was clearly understood and acknowledged by the court; *ibid* at Note 12). The court stated:

> The notion that one who fully discloses and teaches those skilled in the art how to make and use a genus and numerous species there within, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of § 112, first paragraph, appears to result in a hypertechnical application of legalistic prose relating to that provision of the statute.

Ibid at 1019.

The holding in *Johnson* was affirmed by the court in *In re Driscoll*, 562 F.2d 1245, 1250, 195 USPQ 434 (CCPA 1977), which observed (with regard to the court's reversal, in *Johnson*, of the Patent Office's refusal to grant Johnson's application the benefit of an earlier filing date,

based on an alleged lack of written description, in the original application, for the negative proviso):

> In reversing the rejection, the court there observed that the **applicants were merely excising the invention of another, to which they were not entitled, rather than creating an artificial subgenus or claiming new matter.**

Ibid at 1250.

Therefore, Applicant asserts that the recitation of method of treatment in a subject not including rats does not constitute new matter and should not be rejected under 35 U.S.C. 112, first paragraph for the negative limitation. Furthermore, the specification clearly positively recites rats as an alternate element in the specification. Therefore, rats may be explicitly excluded in the claims.

Applicants therefore request removal of this basis for rejection and allowance of claims 18 and 25-26 to issue.

Pursuant to the above amendments and remarks, consideration and allowance of the pending application is believed warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $210.00, representing the fee for a small entity under 37 C.F.R. § 1.17(a)(2), and a Request for Extension

of Time and Declaration are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

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CERTIFICATE OF EXPRESS MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service in an envelope addressed to: MAIL STOP AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Gwendolyn D. Spratt — 6-28-04

Gwendolyn D. Spratt — Date

ATTORNEY DOCKET NO. 23016.0002US
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	
Wynick, David	Art Unit: 1647
Application No. 09/230,463	Examiner: Gucker, S.
Filing Date: January 22, 1999	Confirmation No. 4323
For: "GALANIN"	

DECLARATION UNDER 37 C.F.R. § 1.132

1. I am Professor in the Department of Neurosciences at Case Western Reserve University, Ohio, USA.

2. I have been associated with teaching and research in the subject of Neurosciences for almost thirty years and have published approximately 100 peer-reviewed papers, review articles and chapters during this time. Examples of these publications together with details of my education are given in the short version of my *curriculum vitae* which is attached and shown as Exhibit A.

3. My research relates to neurochemical plasticity in adult neurons. In recent years, my laboratory has focused on the molecules and cells involved in altering neuronal gene expression in response to axonal injury. The galanin peptide has been one molecule of long-standing interest and a major focus of my laboratory.

4. I am familiar with the work of David Wynick in the field of galanin and nerve regeneration.

5. I have reviewed the specification of US Patent Application Serial No. 09/230,463 ("the patent application"). I understand the technology described in the patent application. In

particular, I have reviewed claim 18 of the patent application and its meaning is clear to me.

6. I have also reviewed the publication "The effects of pretreatment with tachykinin antagonists and galanin on the development of spinal cord hyperexcitability following sciatic nerve section in the rat" by Luo, L. and Wiesenfield-Hallin, Z. (1995) Neuropeptides 28 161-166 ("the Luo publication"). I understand the experiments described in that publication and the implications of the data resulting from those experiments.

7. The Luo publication demonstrates that galanin inhibits spinal cord electrical hyper-excitability following nerve section (axotomy) when administered directly into the space surrounding the bottom part of the spinal cord (intrathecal administration to the lumbar enlargement). Such spinal cord excitability, especially after injury, is thought to be related to the development of chronic pain states and blockade of electrical discharge reduces neuropathic pain behaviour. The Luo publication deals exclusively with neuropathic pain behaviour, not with peripheral nerve damage as claimed in the patent application. Peripheral nerve damage is in no way synonymous with chronic neuropathic pain. Further, the actions of galanin when administered directly to the spinal cord (which is part of the central nervous system) to inhibit chronic pain behaviour, in no way implies or predicts regeneration at the level of the sciatic nerve (which is part of the peripheral nervous system).

8. There is no indication in the Luo publication that the treatment of chronic pain is in any way predictive of regeneration of an injured peripheral nerve or, indeed, in the spinal cord. There is no suggestion in the Luo publication that a galanin agonist would be effective in the treatment of peripheral nerve damage in a subject.

9. The patent application provides evidence that galanin has the ability to promote functional nerve regeneration. However, it is highly unlikely that such regeneration would have occurred in the animals used in the experiments of the Luo publication since galanin was administered directly onto the spinal cord. It is most unlikely that the galanin

peptide would reach, or be transported to, the damaged end of the sciatic nerve (which is the closest component of the peripheral nervous system) and thus would not be expected to alter peripheral nerve regeneration. Further, the experiment was begun one hour after spinal transection and, as shown in Figure 3, the galanin experiment was carried out over 150 minutes from the start of the experiment. Therefore, the rats were utilised in the experiment for a maximum of 3.5 hours after decerebration and spinal cord section. This short time period would not be sufficient for functional nerve regeneration to occur in response to the presence of galanin.

10. The results contained in the patent application indicate that, in wild type mice, functional nerve regeneration does not reach significant levels until at least several days after nerve injury (Figure 5). In addition, functional recovery in wild type mice is not complete until approximately three weeks after nerve injury (Figure 6), indicating that effective nerve regeneration and therefore treatment of peripheral nerve damage is a prolonged process.

11. In summary, it is my opinion that the Luo publication does not give any incentive to the person of ordinary skill in the art to attempt a method for the treatment of peripheral nerve damage in a subject in need of such treatment, the method comprising the step of administering to the subject an amount of a galanin agonist effective to treat peripheral nerve damage as recited by the claims of the patent application.

12. I further declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: June 28, 2004

Richard E. Zigmond
Professor Richard E. Zigmond

225362

EXHIBIT A

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
RICHARD E. ZIGMOND	PROFESSOR OF NEUROSCIENCES

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Harvard College, Cambridge MA	BA cum laude	1962-66	Biology
Rockefeller U., NY, grad. stud.with Bruce McEwen	Ph.D.	1966-71	Neuroscience
Rockefeller U., NY, postdoc.with Don Pfaff		1971-72	Neuroendocrinology
U. of Cambridge, UK, postdoc. with Leslie Iversen		1972-75	Neurochemistry
Harvard Medical School/Children's Hospital, (Sabbatical with Michael Greenberg)		2000-01	Molecular Biology

Positions and Honors

__Appointments:__ Assist. Prof. (1975-81), Assoc. Prof. (1981-89) of Pharmacology, Harvard Medical School; Instructor in Neurobiology of Behavior at Cold Spring Harbor Lab. (1979-82); Prof. of Neurosci., Case Western Reserve Univ. (CWRU) School of Medicine (1989-present); Instructor in Neurobiology at Marine Biology Lab. (1981-84); Program Director, NIH Postdoctoral Training Program in Devel. Neurol. (1981-89; Harvard Med. Sch.); Instructor on Review and Update in Neurobiology for Neurosurgeons (1984, 86, 88); Chair, Committee on Appointments and Tenure, Department of Neurosciences, CWRU (1991-present); Chair, Gordon Conference on Neural Plasticity (1991); Program Committee, Society for Neuroscience (1991-93); Acting Chair, Department of Neurosciences, 1992-93).

__Fellowships and Special Grant Awards:__ Pop. Council Fellowship in Mammalian Reproduction (1971-72); British-American Heart Found Fellowship (1972-73); Sloan Found. Fellowship in Neurochem. (1972-74); Klingenstein Fellowship in the Neurosciences (1987-1990); Mellon Found. Faculty Award (1976-1977); NIMH Research Scientist Development Award (1977-87); Javits Neuroscience Investigator Award (1987-94); NIMH Research Scientist Award (1987-94).

__Grant Review Committees:__ External review committee for the Lab. of Developmental Neurobiology NICHD (1985, 1990); Study Section for Tobacco-Related Disease Research Program of the Univ. of California (1993, 1994); Ad hoc Reviewer, Neurology C Study Section (Neuro C; 1995, 1996); Member, Neurological Sciences 1 Study Section (NLS1) and Molecular Developmental and Cellular Neurosciences Study Section (MDCN7; 1996-2000); Reviewer of Research at the Burke Medical Research Institute (1998).

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<u>**Editorial Boards:**</u> *J. Neurosci. Meth.* (1978-1998), *J. Neurosci.* (1985-91), *Ann. Rev. Neurosci.* (1986-90), *TINS* (1986-90), *New Biol.* (1989-91), *Adv. in Neurosci.* (1989-present), *Neuroscience* (1996-present), *J. Mol. Neurosci.* (1997-present), *Autonomic Neuroscience: Basic and Clinical* (formerly *J. Auton. Nerv. Syst.* (1998-), *NeuroSignals* (formerly *Biological Signals and Receptors* (2001-present).

Selected peer-reviewed publications since 1998.

1. Rao MS, Sun Y, Escary JL, Perreau J, Patterson PH, Zigmond RE, Brulet P, Landis SC. Leukemia inhibitory factor mediates an injury response but not a developmental transmitter switch in sympathetic neurons. Neuron <u>11</u>:1175-1185, 1993.
2. Sun Y, Rao MS, Zigmond RE, Landis SC. Regulation of vasoactive intestinal peptide expression in sympathetic neurons in culture and after axotomy: The role of cholinergic differentiation factor/leukemia inhibitory factor. J Neurobiol <u>25</u>:415-430, 1994.
3. RC, Shadiack AM, Bennett TA, Sedwick CE, Zigmond RE. Changes in the macrophage population of the rat superior cervical ganglion after postganglionic nerve injury. J Neurobiol <u>27</u>:141-153, 1994.
4. Sun Y, Landis S, Zigmond R. Signals triggering the induction of leukemia inhibitory factor in sympathetic superior cervical ganglia and their nerve trunks after axonal injury. Mol Cell Neurosci <u>7</u>:152-163, 1996.
5. Hyatt-Sachs H, Bachoo M, Schreiber R, Vaccariello SA, Zigmond RE. Chemical sympathectomy and postganglionic nerve transection similarly increase galanin and VIP mRNA but not the peptides themselves. J Neurobiol <u>30</u>:543-555, 1996.
6. Sun Y, Zigmond RE. Leukemia inhibitory factor induced in the sciatic nerve after axotomy is involved in the induction of galanin in sensory neurons. Europ J Neurosci <u>8</u>:2213-2220, 1996.
7. Zigmond, RE. Retrograde and paracrine influences on neuropeptide expression in sympathetic neurons after axonal injury. In: <u>Cytokines and the CNS: Development, Defenses and Disease</u> (RM Ransohoff, EN Benveniste, Eds) CRC Press, Boca Raton, pp. 169-186, 1996.
8. Zigmond RE, Hyatt-Sachs H, Mohney RP, Schreiber RC, Shadiack AM, Sun Y, Vaccariello SA. Changes in neuropeptide phenotype after axotomy of adult peripheral neurons and the role of leukemia inhibitory factor. Perspec Dev Neurobiol <u>4</u>:75-90, 1996.
9. Zhou Y, Deneris E, Zigmond RE. Differential regulation of levels of nicotinic receptor subunit transcripts in adult sympathetic neurons after axotomy. J Neurobiol <u>34</u>:164-178, 1998.
10. Shadiack AM, Zigmond RE. Galanin induced in sympathetic neurons after axotomy is anterogradely transported toward regenerating nerve endings. Neuropeptides <u>32</u>:257-264, 1998.
11. Shadiack AM, Vaccariello SA, Sun Y, Zigmond RE. Nerve growth factor inhibits sympathetic neuron's response to an injury cytokine. Proc Natl Acad Sci USA <u>95</u>:7727-7730, 1998.
12. Mohney RP, Zigmond RE. Vasoactive intestinal peptide enhances its own expression in sympathetic neurons after injury. J Neurosci <u>18</u>:5285-5293, 1998.
13. Zigmond RE, Mohney RP, Schreiber RC, Shadiack, AM, Sun Y, Vaccarriello SA, Zhou Y. Plasticity in gene expression in adult sympathetic neurons after axonal damage. Adv in Pharmacol 42:899-903, 1998.
14. Nagamoto-Combs K, Vaccariello S, Zigmond RE. The levels of LIF mRNA in a Schwann cell line are regulated by multiple second messenger pathways. J Neurochem <u>72</u>:1871-1881, 1999.
15. Mohney RP, Zigmond RE. Galanin expression is decreased by cAMP-elevating agents in cultured sympathetic ganglia. NeuroReport <u>10</u>:1221-1224, 1999.

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16. Rittenhouse A R., Zigmond RE. The role of N- and L-type calcium channels in the depolarization-induced activation of tyrosine hydroxylase and release of norepinephrine by sympathetic cell bodies and nerve terminals. J Neurobiol 40:137-148, 1999.
17. Boeshore KL, Luckey CN, Zigmond RE, Large TH. TrkB isoforms with distinct neurotrophin specificities are expressed in predominantly non-overlapping populations of avian dorsal root ganglion neurons. J Neurosci 19:4739-4747, 1999.
18. Ip NY, Zigmond RE. Synergistic effects of muscarinic agonists and secretin or vasoactive intestinal peptides on the regulation of tyrosine hydroxylase activity in sympathetic neurons. J Neurobiol 42:14-21, 2000.
19. Bibevski S, Zhou Y, McIntosh J, Zigmond R, Dunlap M. Functional nicotinic acetylchoine receptors that mediate ganglionic transmission in cardiac parasympathetic neurons. J. Neurosci 20:5076-5082, 2000.
20. Zigmond RE. Neuropeptide action in sympathetic ganglia: Evidence for distinct functions in intact and axotomized ganglia. Ann N Y Acad Sci.921:103-108, 2000.
21. Shadiack A, Sun Y, Zigmond R. Nerve growth factor antiserum induces axotomy-like changes in neuropeptide expression in intact sympathetic and sensory neurons. J. Neurosci. 21:363-371, 2001.
22. Zhou Y, Deneris E, Zigmond R. Nicotinic acetylcholine receptor subunit proteins alpha7 and beta4 decrease in the superior cervical ganglion after axotomy. J Neurobiol. 46: 178-192, 2001.
23. Schreiber RC, Krivacic K, Kirby, B, Vaccariello SA, Tani M, Ransohoff RM, and Zigmond RE. Monocyte chemoattractant peptide- 1(MCP-1) is rapidly expressed by sympathetic ganglion neurons following axonal injury. NeuroReport 12:601-606, 2001.
24. Zigmond RE. Can galanin also be considered as growth-associated protein 3.2? TINS 24:494-496, 2001.
25. Takasu, AM. Dalva MB, Zigmond R, Greenberg, ME. Science. EphB receptors modulate NMDA receptor-dependent calcium influx and gene expression. Science 295: 491-495, 2002.
26. Schreiber RC, Boeshore K, Vaccariello SA, Shadiack, Zigmond RE. A comparison of the changes in the non-neuronal cell populations of the superior cervical ganglia following decentralization and axotomy. J. Neurobiol. 53: 68-79, 2002.
27. Zigmond R.E. Plasticity in the autonomic nervous system: Responses of adult sympathetic neurons to injury. In: Handbook of Autonomic Nervous System in Health and Disease (J Licinio and L Bolis, Eds) Marcel Dekker, New York, pp. 167-184, 2002.

Research Support

Sponsor: National Institutes of Health **Award Number:** NS12651
Dates: 7/1/2003-6/30/2004 **Amounts:** Current Direct Costs: 0
Title: Experience and the Neurochemistry of the Synapse
Percent Effort: 35%
Brief description of the project: To identity the transmitter responsible for the non-cholinergic activation of TH in the SCG after preganglionic nerve stimulation, determine whether such nerve stimulation alters neuropeptide expression, determine whether PACAP and VIP are involved in feedback mechanisms regulating their own expression, examine the signals triggering the changes in nAChR receptor subunit mRNA expression in axotomized SCG neurons, determine if changes occur at the receptor level, and ask whether a phenomenon comparable to "disuse supersensitivity" is seen in these receptors as a result of changes in afferent nerve stimulation.

EXHIBIT A

4

Sponsor: National Institutes of Health **Award Numbers:** NS17512
Dates: 5/15/03-4/30/07 **Amounts:** Current Direct Costs: $237,500
Title: Recovery of Function after Neural Damage
Percent Effort: 35%

Brief description of the project: To determine the cellular and molecular changes that occur in peripheral neurons in the context of regeneration. We have been notified by the NINDS that this application will be refunded.